Contrast induced AKI in Diabetics

By

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Epidemiology

•3rd cause of hospital-acquired (AKI) after impaired renal perfusion and use of nephrotoxic medications.

•CIN can result from intravenous or intra-arterial injections of iodine-based contrast media (CM) during enhanced X-ray and computerized tomography (CT) imaging examinations, or coronary artery interventions.

1. DEFINITION OF CI-AKI

Contrast-Induced AKI (CI-AKI) is defined as a rise in serum creatinine of ≥ 0.5 mg/dl (≥44 µmol/L) or a 25% increase from baseline value, assessed at 48 hours after a radiological procedure without an alternative etiology.

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney inter., Suppl.* 2012; 2: 1–138.

2. RISK STRATIFICATION (RENAL)

- **Low Risk: eGFR > 60 ml/min**
- **Moderate Risk: eGFR 30-59 ml/min**
- **High Risk: eGFR < 30ml/min**

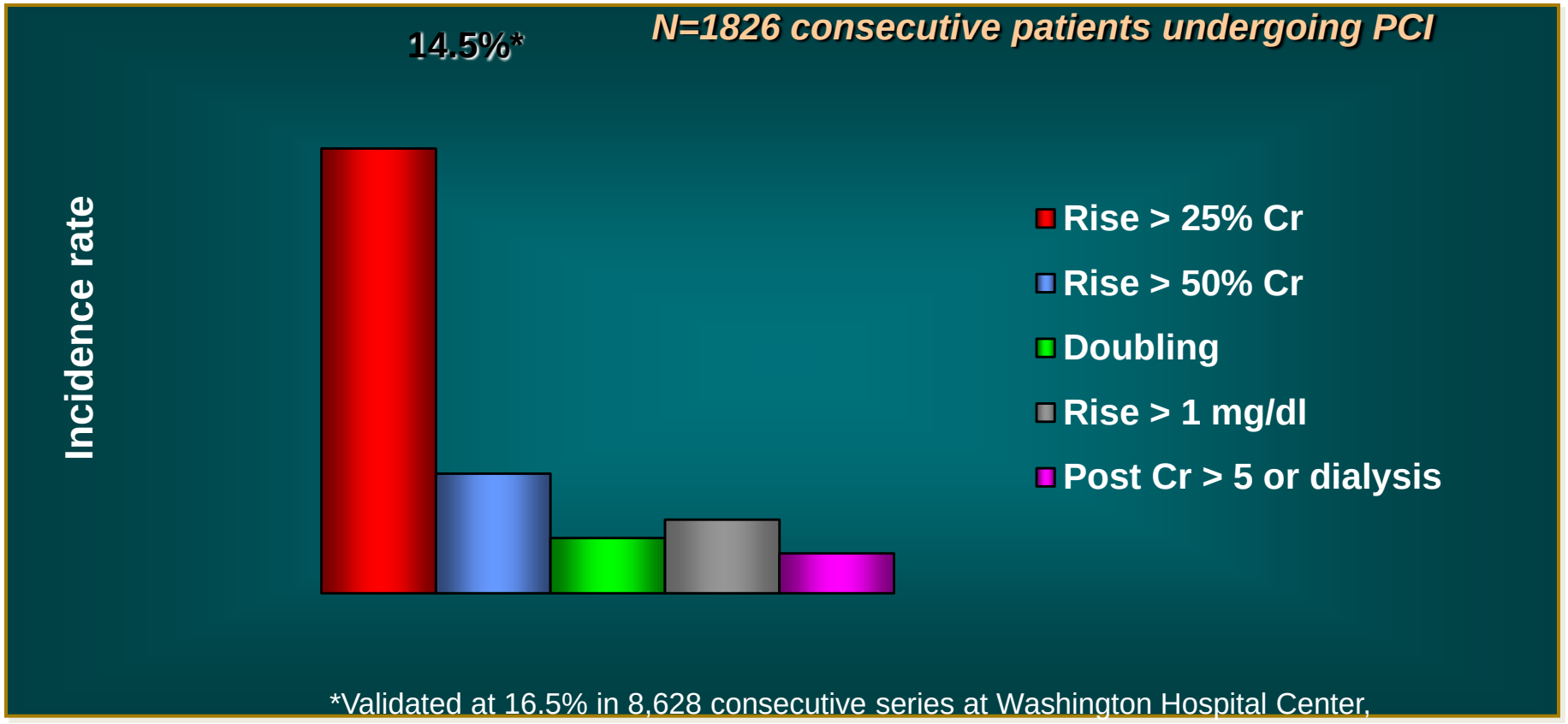
- Estimated Glomerular Filtration Rate (eGFR) should be computed using the CKD-EPI formula which has been validated locally.

Risk factors	Integer score (calculate)
Hypotension	5
IABP	5
CHF	5
Age >75 years	4
Anemia	3
Diabetes	3
Contrast-media volume	1 per 100 ml
SCr >1.5 mg/dl (>132.6 μmol/l)	4
or	
eGFR <60 ml/min per 1.73 m^2	2 for 40-60 4 for 20-39 6 for <20

Note: Low risk: cumulative score <5, high risk: cumulative score >16

Mehran R, Aymong ED, Nikolsky E et al: A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004; 44: 1393–1399

Frequency of Contrast-Induced Nephropathy



McCullough PA, *Am J Med* 1997;103:386-375.

Risk factors for contrast induced nephropathy.

Patient-related risk factors

Preexisting kidney disease

Diabetes with chronic kidney disease

Age > 75 y

Dehydration[a]

Hypoalbuminemia (<35 g/L)[a]

Poor heart function or hemodynamic instability[a]

- Preprocedure intra-aortic balloon pump
- Anemia or postprocedure drop in hematocrit
- Hypotension
- Advanced heart failure
- Left ventricular ejection fracture <40%
- Acute myocardial infarction or increased CK-MB
- Need for cardiac surgery after contrast exposure
- Urgent or emergent procedure

Peripheral vascular disease

Concurrent nephrotoxic medication[a]

- NSAIDs, aminoglycoside, amphotericin B, high-dose diuretics, antiviral drugs such as acyclovir and foscarnet, cyclosporine A

New risk factors[a]

- Metabolic syndrome
- Prediabetic condition
- Hyperuricemia

Procedure-related risk factors

Type of CM[a]

High-osmolar CM

Ionic vs. non-ionic CM

High-viscosity CM

High volume of CM[a]

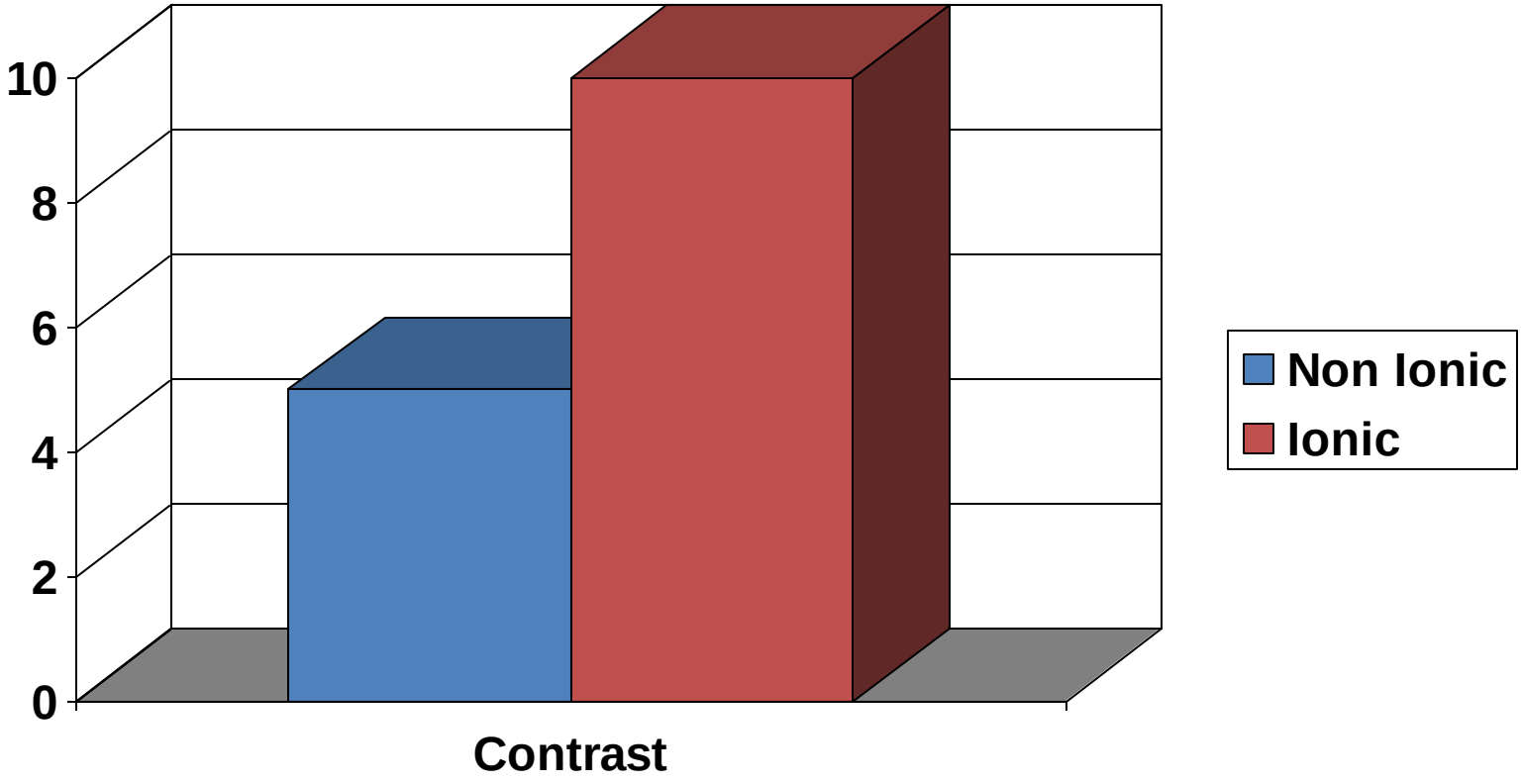
Multiple CM injections within 72 h[a]

Intra-arterial vs. intravenous injection

Conflicting (doubtful) risk factors

- Female
- Multiple myoloma
- Cirrhosis
- Use of ACEI or ARB[a]
- Renal transplant
- Diabetes with normal renal function
- Low-osmolar CM in high-risk patients[a]

Effects of Ionic vs Non Ionic Contrast on Renal Function post angiography-Gomes et al:Radiology 1989



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Canadian Association of Radiologists Journal 65 (2014) 96–105

CANADIAN ASSOCIATION OF RADIOLOGISTS JOURNAL

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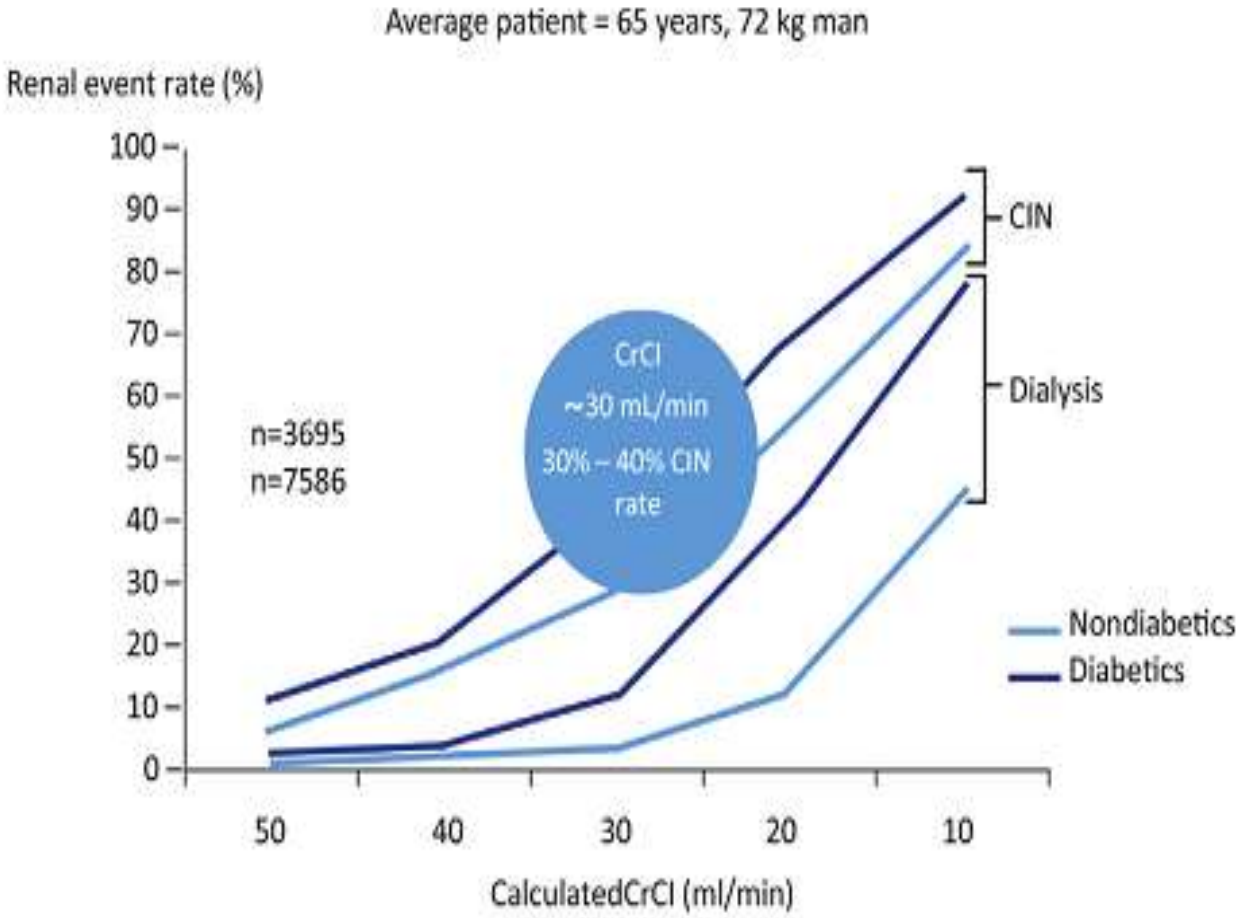
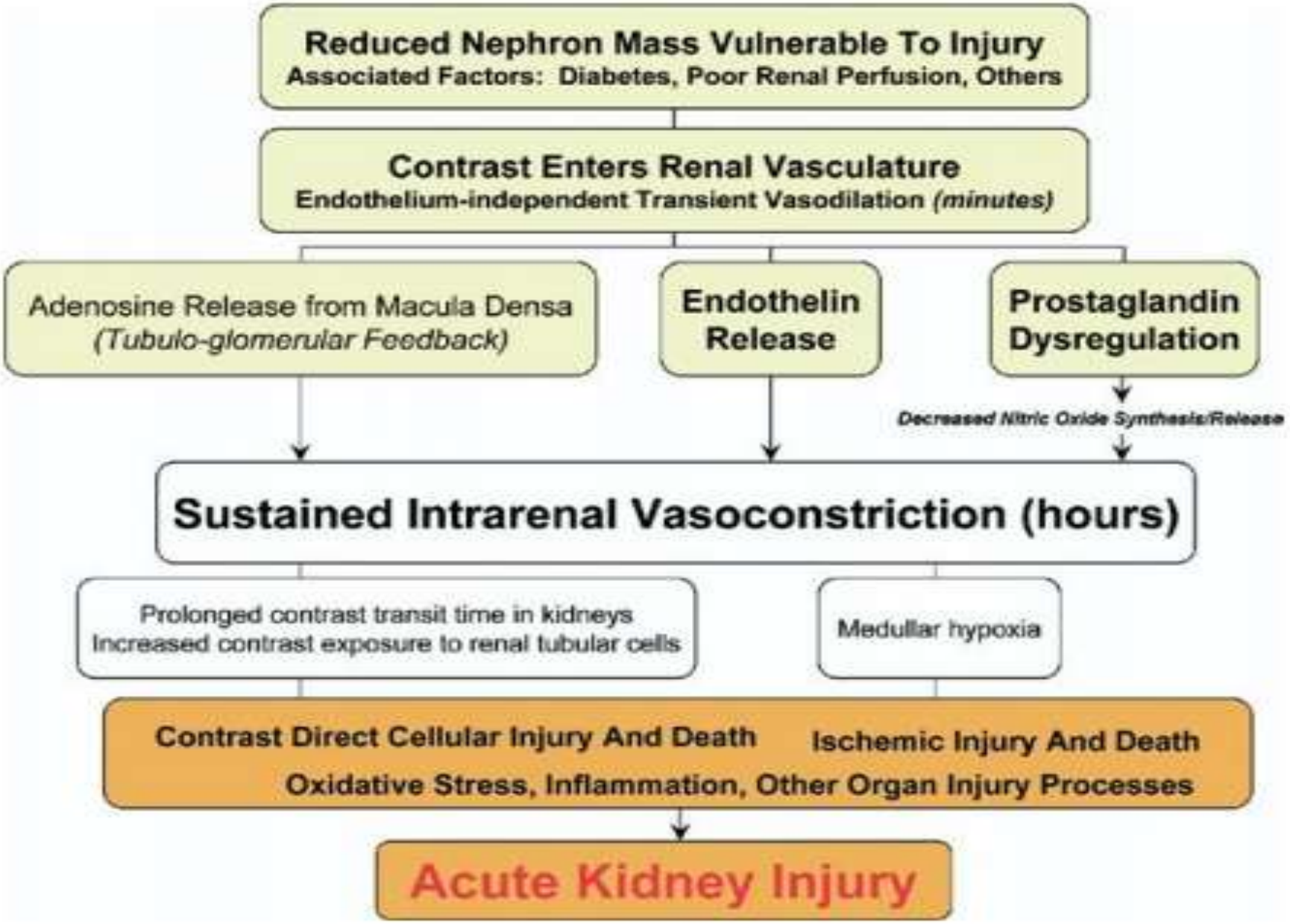
Critically Appraised Topic / Évaluation critique

Canadian Association of Radiologists Consensus Guidelines for the Prevention of Contrast-Induced Nephropathy: Update 2012

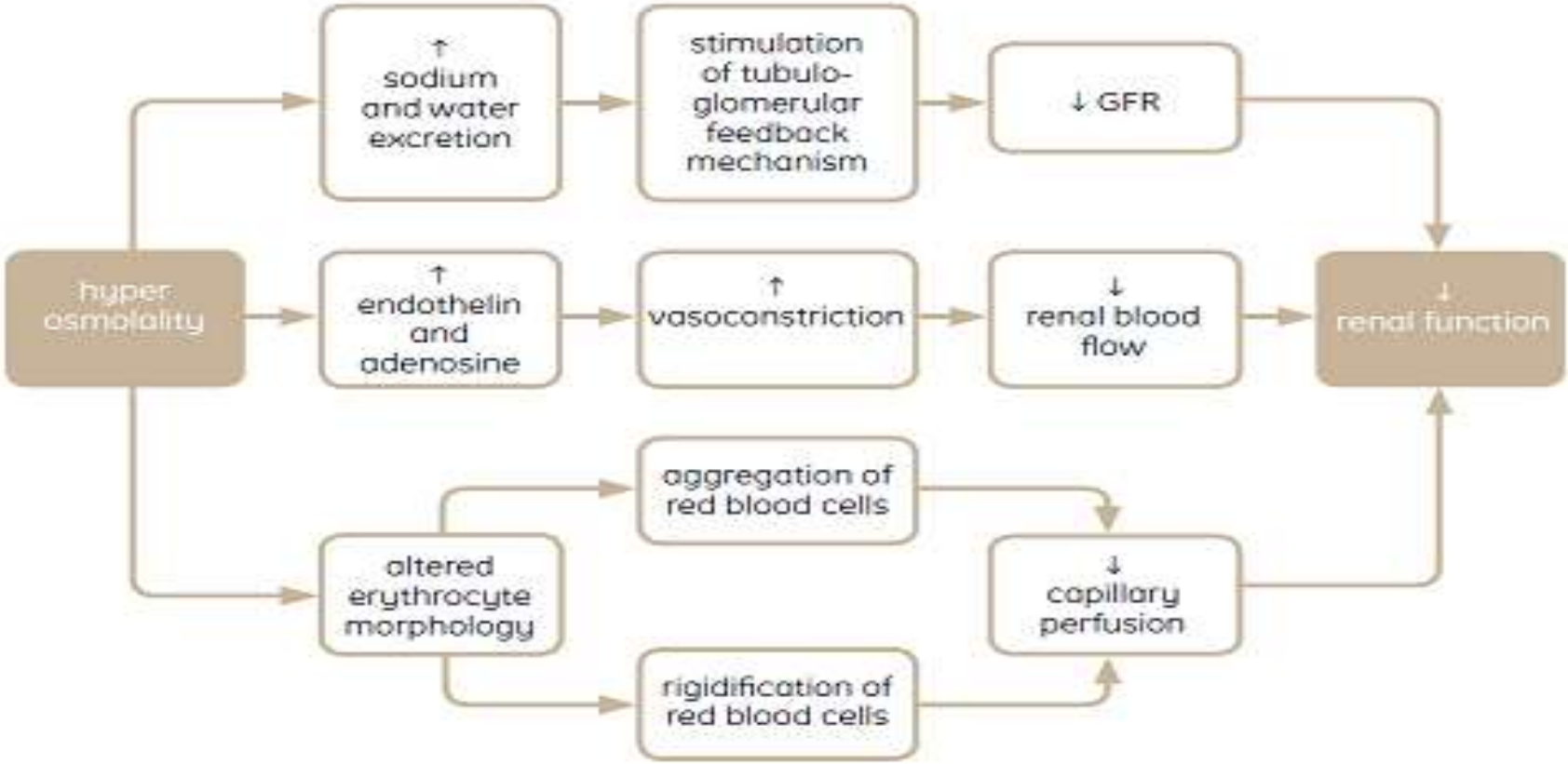


PATHOPHYSIOLOGY



Osmolality and Nephrotoxicity

How osmolality might influence the development of contrast-induced nephropathy (CIN)[1-4]



Adapted from Berg 2000[1], Gleeson 2004[2], Kerl 2008[3], Jung 2008[4]

Then what about DM?

Hindawi Publishing Corporation
BioMed Research International
Volume 2013, Article ID 123589, 8 pages
http://dx.doi.org/10.1155/2013/123589

Review Article

Why Is Diabetes Mellitus a Risk Factor for Contrast-Induced Nephropathy?

The special structure of the renal medulla, designed for urinary concentrating capability, is the cause for low outer medullary oxygen tension (pO_2), at the range of 30–40 mmHg under normal physiologic conditions. Low medullary oxygenation reflects intense tubular transport (particularly by medullary thick limbs, mTALs) in a region with limited blood and oxygen supply [7]. Highly efficient neurohumoral mechanisms maintain barely balanced medullary oxygenation by matching regional tubular transport activity and blood supply. Medullary tubular transport activity is governed by solute delivery to the distal nephron (determined by GFR and proximal tubular transport) and by the direct regulation of mTAL transporters, particularly Na-K ATPase. Blood and oxygen supply, delivered through per-

related to intensified renal hypoxia and oxidative stress, as reviewed in depth in [17]. Indeed, experimental diabetes is associated with reduced renal pO_2. Using oxygen microelectrodes, Palm and colleagues [18] demonstrated lower renal parenchymal pO_2 in diabetic rats, as compared with control animals, both in the cortex (about 36 versus 50 mmHg) and in the medulla (around 11 versus 27 mmHg). This observation

inducible factors (HIFs). HIFs are key regulators of cellular response to hypoxic stress, controlling the expression of numerous genes involved in cell metabolism, proliferation, and survival and in the structure and function of regional microcirculation. Under physiologic conditions, HIF subunit α undergoes proteasomal degradation, initiated by oxygen-sensitive HIF-prolyl hydroxylases. Intensified hypoxia deactivates HIF-prolyl hydroxylases, leading to HIF-α accumulation and its binding to HIF-β subunits. The formed HIF-$\alpha\beta$ heterodimer undergoes nuclear translocation, binds to hypoxia-response elements (HRE) along the DNA strands, and initiates transcriptional responses [9]. Indeed, nuclear

WHERE?

[13]. In these models, inhibition of prostaglandin or NO synthesis abolishes outer medullary vasodilatory response to the radiocontrast and intensifies medullary hypoxia, leading to AKI with outer medullary hypoxic damage. Tubular injury, ranging from apoptosis to frank necrosis, mostly affects mTALs in the inner stripe of the outer medulla. However, in the most severe models damage may extend outwards to the outer stripe and medullary rays and inwards into the papilla, involving S3 segments of the proximal tubules, as well as thin limbs, and collecting ducts, respectively. Within the

Villains?

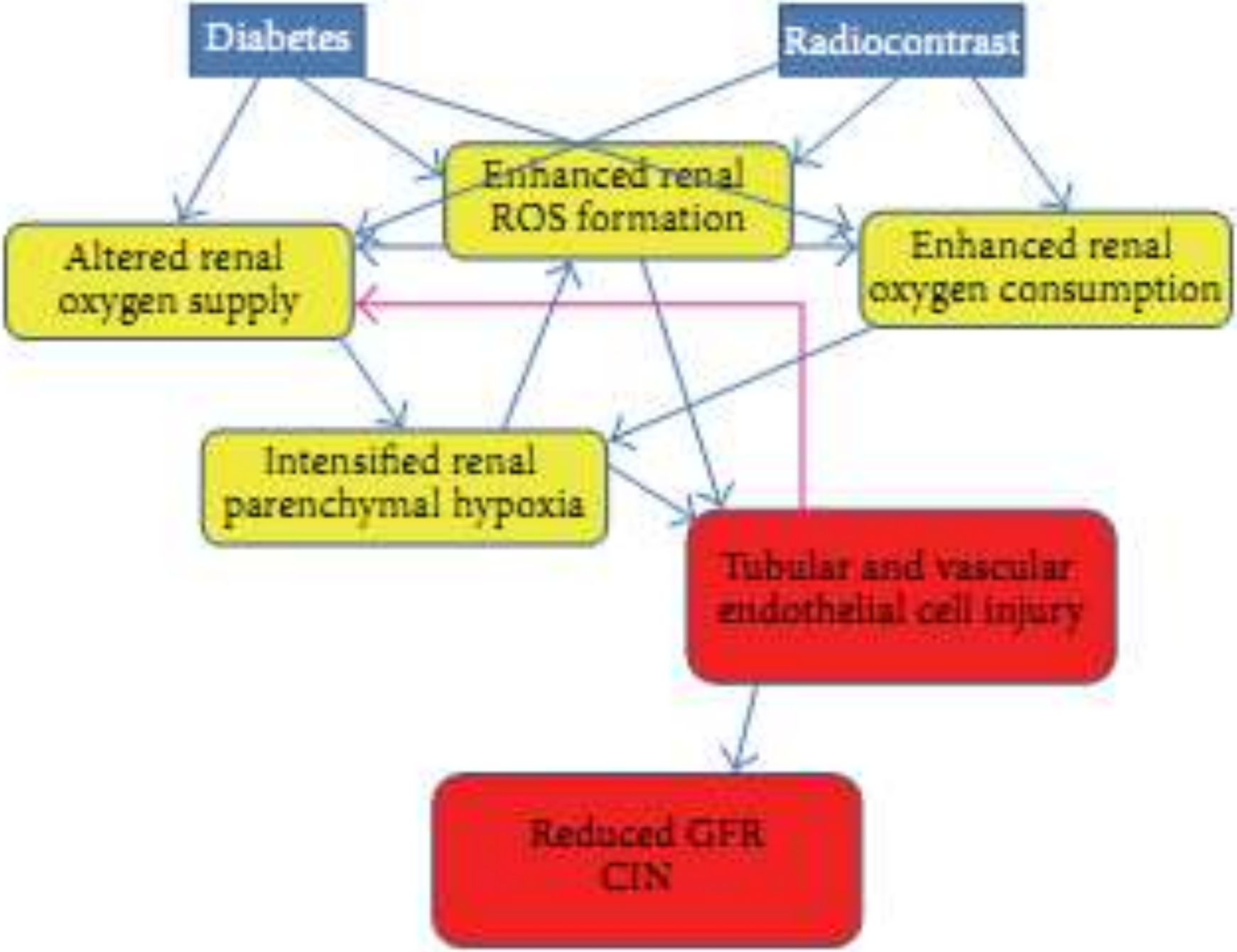
1- ET1

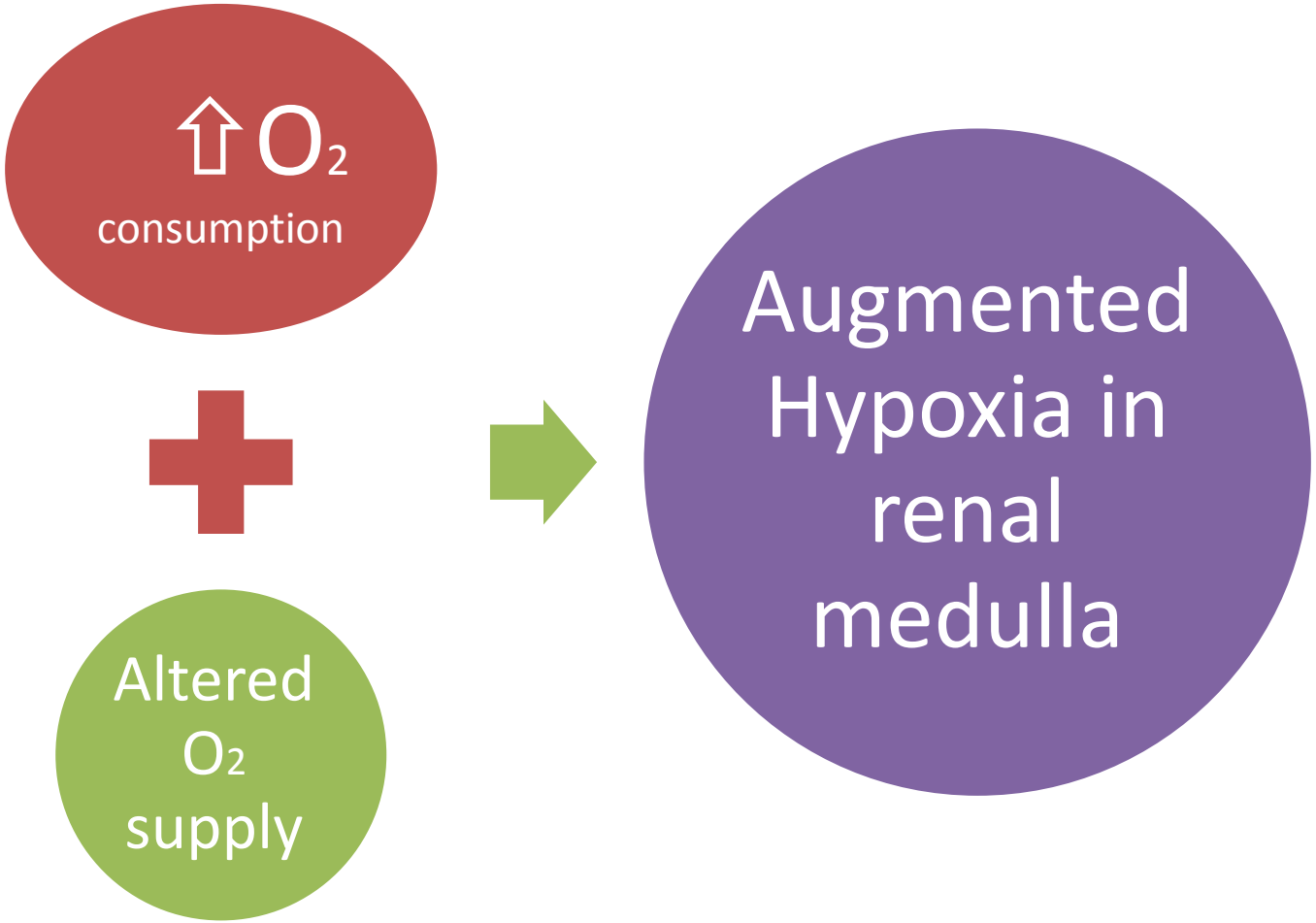
endothelin-1 (ET-1) under experimental settings [34]. ET-1 levels also increase following radiocontrast administration and are higher both at baseline and following radiocontrast in diabetics and in patients with CKD [35]. Diabetes is associated with enhanced synthesis of the pre-pro-hormone. In addition, endothelin-converting enzyme (ECE)-1, which

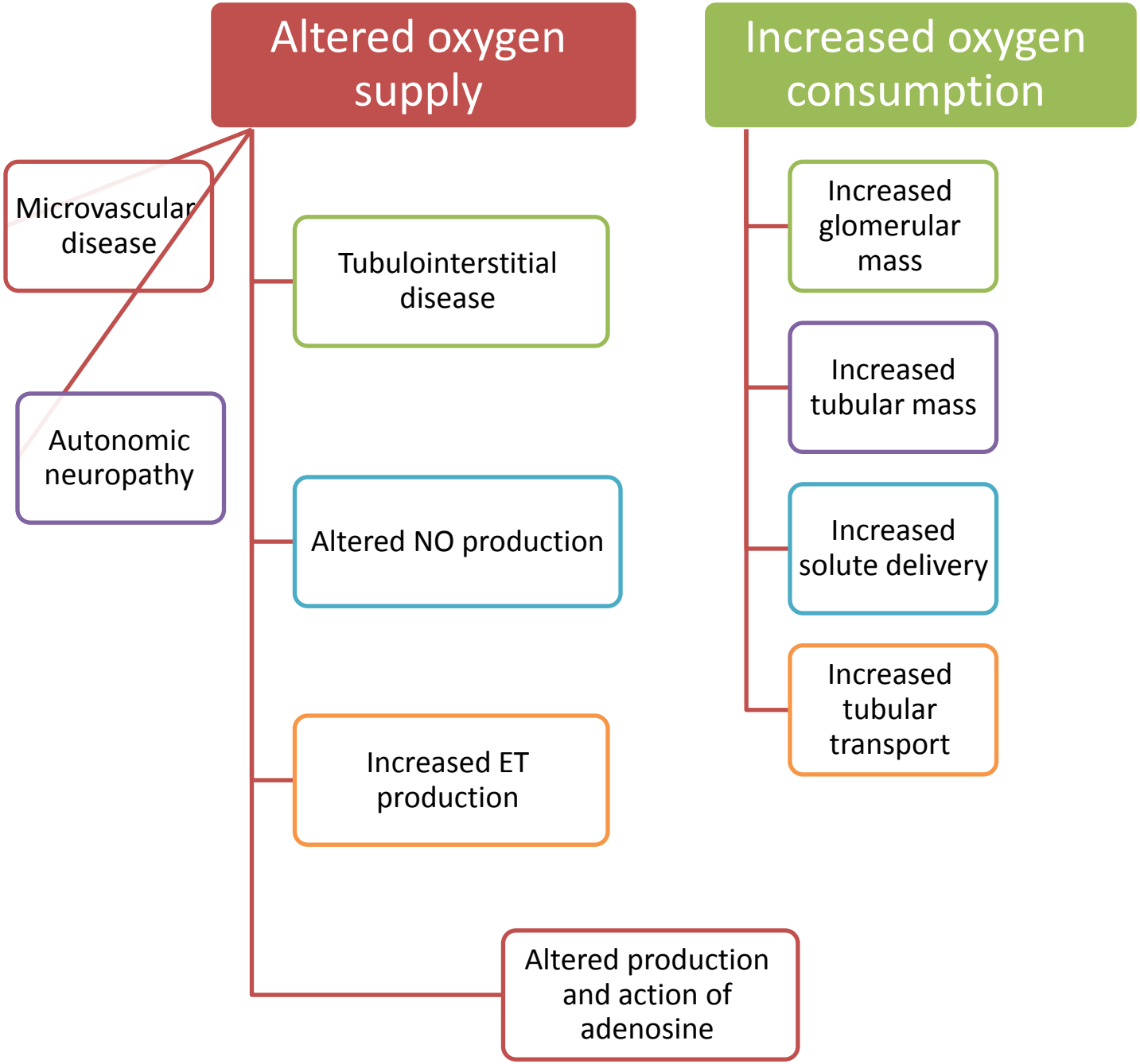
compound ET-1, is also upregulated in diabetes. Experimental diabetes in rats resulted in a fivefold increase in ECE-1 expression in the outer medulla, and a 15-fold increment was noted in diabetic rats subjected to contrast medium [36]. Conceivably, radiocontrast-induced enhanced production of ET-1, particularly in the diabetic kidney, by both the induction of prehormone and ECE-1 synthesis, participates in microvascular dysregulation and in the development of CIN. PKC, activated in diabetes [37], is a known mediator of ECE-1 activation [38]. Furthermore, ECE-1 is likely a HIF-target gene [39], and possibly enhanced medullary ECE-1 is triggered by HIF, induced by both diabetes and contrast media.

2-Adenosine

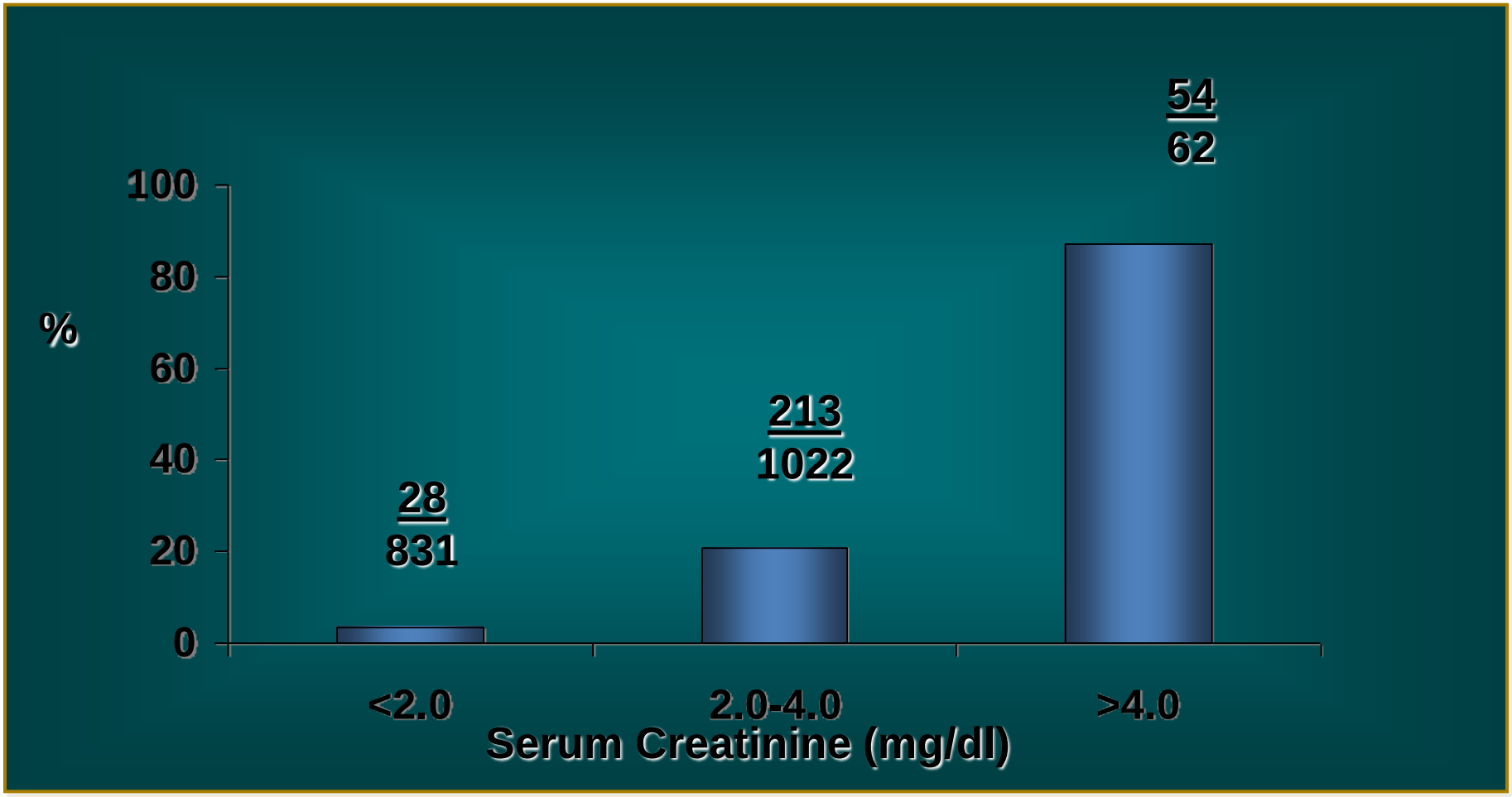
Adenosine-induced enhancement of proximal tubular reabsorption and inhibition of mTAL transport activity improve medullary oxygenation. However, its microvascular effects are more complex regarding medullary oxygenation, exerting both vascular constriction (via adenosine A1 receptors) and vascular dilatation (stimulated by adenosine A2 receptors). Some vascular beds, such as descending vasa recta, express both types of receptors [40]. The diverse and complex effects of adenosine on the renal microcirculation can be demonstrated by its exogenous administration in the presence of selective adenosine inhibitors, illustrating an overall reduction of cortical microcirculation and oxygenation and amelioration of medullary hypoxia [41]. Yet endogenously generated adenosine may exert quite different vascular responses, and altered NO synthesis or increased angiotensin II might modify their overall activity, potentiating vasoconstriction


Diabetes
Radiocontrast
Enhanced renal ROS formation
Altered renal oxygen supply
Enhanced renal oxygen consumption
Intensified renal parenchymal hypoxia
Tubular and vascular endothelial cell injury
Reduced GFR CIN


⇧O2
consumption
Altered
O2
supply
Augmented
Hypoxia in
renal
medulla


Altered oxygen supply
Increased oxygen consumption
Microvascular disease
Autonomic neuropathy
Tubulointerstitial disease
Altered NO production
Increased ET production
Altered production and action of adenosine
Increased glomerular mass
Increased tubular mass
Increased solute delivery
Increased tubular transport

Incidence of Contrast Induced Renal Dysfunction in Diabetic Patients



Berns A, *Kidney International*, 1987

PREVENTION

Strategies to prevent contrast-induced nephropathy in high-risk patients.

Evaluation of the risk for CIN and benefit of examination in all patients
Consider alternative imaging methods in patients at high risk of CIN
Drug review
Nonpharmacological prevention strategies
Use lowest possible dose
Use IOCM or LOCM except Ioxaglate or Iohexol
Avoid repeat injection within 72 h
Pharmacological prevention strategies
IV volume expansion with isotonic NaCl or $NaHCO_3$
Oral *N*-acetylcysteine with IV volume expansion
Hemodialysis or hemofiltration for CKD 4/5 with functional access
Policy to perform electronic alertness

7. ALGORITHM FOR CLASSIFICATION AND INTERVENTION

CALCULATE eGFR USING CKD-EPI

DISCONTINUE NSAIDS, AMINOGLYCOSIDES, METFORMIN, ANTI-VIRALS, AMPHOTERICIN B, ACE-INHIBITORS, ARBS IF POSSIBLE

High Risk eGFR < 30ml/min

- Consider admission
- Refer to Nephrology service
- Start IV hydration (see Guideline 5)
- Preferred Contrast Media (CM):ISOSMOLAR
- Limit and specify CM volume: < 30 ml for diagnostic procedures and <100 ml for diagnostic procedures + interventional procedures
- Give NAC 600-1200 mg PO BID for 3 days (1 day before until 1 day after the procedure)

Moderate Risk eGFR 30-59 ml/min

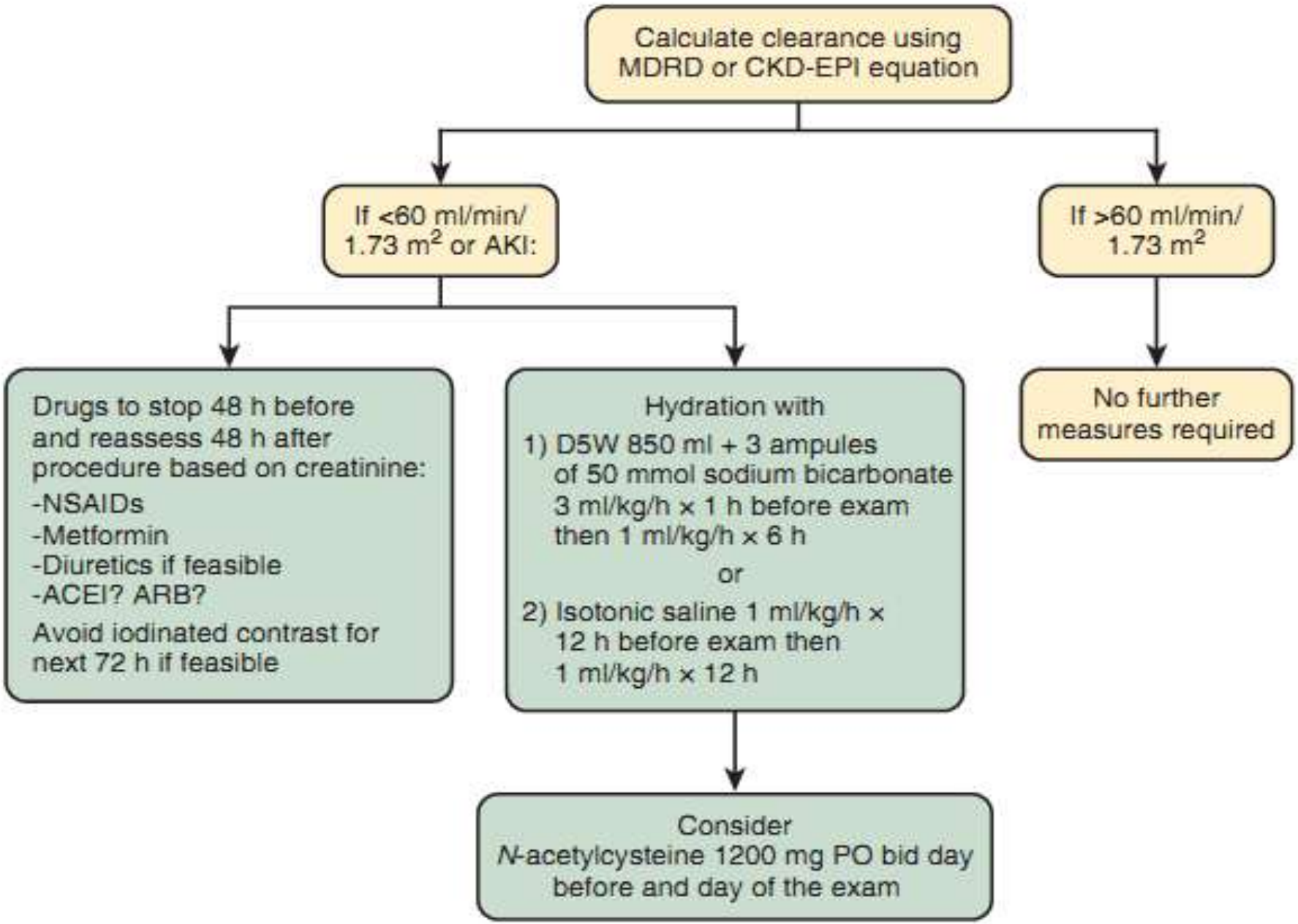
- Consider Nephrology referral
- Start IV hydration (see Guideline 5)
- Preferred Contrast Media (CM): ISOSMOLAR
- for intra-arterial procedures.
- Limit and specify CM volume: < 30 ml for diagnostic procedures and <100 ml for diagnostic procedures+ interventional procedures
- Give NAC 600-1200 mg PO BID for 3 days (1 day before until 1 day after the procedure)

Low Risk eGFR > 60 ml/min

- Oral hydration should be advised (see Guideline 5).
- May give NAC 600-1200 mg PO BID for 3 days (1 day before until 1 day after the procedure).

Modified from Mc Cullough PA. Contrast-Induced Acute Kidney Injury. JACC 2008;51:1419-28

Management of Patients Receiving Iodinated Contrast Media



3. CONTRAST MEDIUM

We recommend the use of either ***Isosmolar or Low Osmolar*** iodinated contrast media, rather than High Osmolar iodinated contrast media in patients at increased risk of CI-AKI.

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney inter.*, Suppl. 2012; 2: 1–138

- **ISOSMOLAR *Iodinated*** contrast media is recommended for the following groups of patients:
  - All high risk patients (eGFR <30 mL/min)
  - Dialysis patients
  - Moderate Risk (eGFR <60 mL/min) patients for intra-arterial procedures
- Use the lowest possible dose of contrast medium in patients at risk for CI-AKI.

For most patients, metformin should be stopped at the time of contrast administration

There is some controversy about when to stop and restart metformin for patients scheduled to undergo intravenous contrast-enhanced examinations.[4] The guidelines from the Canadian Association of Radiologists[2] state that patients taking metformin who have an estimated glomerular filtration rate (eGFR) of less than 60 mL/min should stop taking metformin at the time of contrast administration. The European Society of Urogenital Radiology advocates stopping metformin 48 hours before CT for patients with an eGFR of less than 45 mL/min.[5]

Restarting metformin depends on renal function and the volume of contrast used

Guidelines from the Canadian Association of Radiologists[2] state that patients taking metformin who have an eGFR of less than 60 mL/min should restart the drug no sooner than 48 hours after contrast administration and only if renal function remains stable (< 25% increase in creatinine above baseline). Patients with an eGFR above 60 mL/min who receive a larger amount of intravenous contrast (> 100 mL; e.g., CT of the abdomen or pelvis, CT angiography of the aorta or lower extremities) should restart metformin no earlier than 48 hours after the procedure.[3]

For small volumes of contrast, patients with normal renal function taking metformin may not require any changes in care

If patients with normal renal function who are taking metformin receive less than 100 mL of intravenous contrast (e.g., enhanced CT of the brain), stopping metformin and/or rechecking creatinine levels 48 hours after the procedure may be unnecessary, because the risk of contrast-induced nephropathy in patients with normal renal function is very low.[5]

MANAGEMENT OF PATIENTS ON RRT

For dialysis patients, use of Isosmolar contrast media is recommende
to minimize the risk of potential volume overload from the performan
of angiographic studies.

If with residual renal function, may give NAC 600-1200 mg PO BID for
days (1 day before until 1 day after the procedure)

Contrast media are dialyzable (HD and PD)

- Schedule HD after the procedure.
- Additional PD exchange/s should be done immediately after the
  procedure.

MONITORING

Repeat serum creatinine at the following time points after CM administration to monitor for CI-AKI

- INPATIENT : 12 hours and 48 hours
- OUTPATIENT : 48 hours
- If with evidence of CI-AKI, consider serial monitoring on days 3-5 post CM administration

Clinical parameters

- Monitor urine output and watch out for subtle signs of uremia (hiccups, tremors, nausea, decreased appetite) which may signify the onset of CI-AKI

DOCTOR'S ORDERS

NAME OF PATIENT: _____ AGE/SEX: _____
ROOM NO.: _____ HOSPITAL NO.: _____
ATTENDING PHYSICIAN: _____

DATE OF PROCEDURE: _____
PROCEDURE: _____

- SERUM CREATININE: ____ RACE: ____ eGFR by CKD-EPI: ____
- RISK STRATIFICATION (Please check):
  - Low: eGFR - > 60 mL/min
  - Moderate: eGFR - 30-59 mL/minnge)
  - High: eGFR - < 30 mL/min
- DISCONTINUE THE FOLLOWING MEDICATIONS (Please check and specify):
  - NSAIDS: ____
  - DIURETICS: ____
  - AMINOGLYCOSIDES: ____
  - ANTI-VIRALS (Foscarnet and Acyclovir): ____
  - AMPHOTERICIN B: ____
  - METFORMIN: ____
  - ACE-INHIBITORS: ____
  - ARBS: ____
  - OTHERS: ____
- START THE FOLLOWING (Please check):
  - N-Acetylcysteine1200 mg PO BID pre and post procedure
  - Others: ____
- INITIATE HYDRATION PROTOCOL (Please check):
  - Oral - 1-2 liters of water 12 hours before the procedure
  - IV - ≥ 1.0-1.5 ml/kg/h of NSS has to be administered for 3–12 hours before and up to 6–12 hours after contrast-media exposure.
  - Others: ____
- USE THE FOLLOWING CONTRAST MEDIUM(Please check):
  - Isoosmolar (Iodixanol)
  - Low osmolar (Iohexol, Iopamidol, Iosaglate, Ioversol)
- REPEAT SERUM CREATININE (Please check):
  - After 12 hours
  - After 48 hours for OPD patients
  - Others: _____
- NEXT HEMODIALYSIS SCHEDULE ON: _____
- ADDITIONAL PD EXCHANGE/S: _____
- REFER TO NEPHROLOGY: _____

ACCOMPLISHED BY (name and signature): _____
DATE: _____ TIME: _____

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Journal of the Chinese Medical Association 76 (2013) 673–681

www.jcma-online.com

Review Article

Current concepts of contrast-induced nephropathy: A brief review

- It is well documented that a higher volume of CM is associated with a higher risk of CIN. Even relatively low doses of CM (<100 mL) can result in permanent renal failure and the need for dialysis in patients with CKD, and each 100-mL increment in contrast volume has been shown to result in a 30% increase in the propability of CIN.

- The current guidelines of the American College of Cardiology/American Heart Association recommend the use of either IOCMs or LOCMs other than iohexol and ioxaglate in patients with CKD undergoing angiography.

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Critically Appraised Topic / Évaluation critique

Canadian Association of Radiologists Consensus Guidelines for the Prevention of Contrast-Induced Nephropathy: Update 2012

- **Prophylactic Dialysis or Hemofiltration**

CM can be easily removed with hemodialysis; however, there is no evidence that this removal reduces the risk of CIN. Reduction of CIN with dialysis is also not biologically plausible because the CM would reach the kidneys within 1or 2 cardiac cycles, and subsequent removal of CM is unlikely to stop the cascade of renal injury, which would have already begun.

Nephrol Dial Transplant (2012) 0: 1–10
doi: 10.1093/ndt/gfs375

NDT
Nephrology Dialysis Transplantation

NDT Perspectives

A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury: Part 1: definitions, conservative management and contrast-induced nephropathy†

Pharmacological prevention strategies of CIN

3.4.1 We recommend volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no volume expansion, in patients at increased risk for CIN. (1A)

3.4.2 We suggest using the oral route for hydration, on the premise that adequate intake of fluid and salt are assured. (2C)

We suggest that, when oral intake of fluid and salt is deemed cumbersome in patients at increased risk of CIN, hydration should be performed by intravenous route. (2C)

3.4.3 We suggest using oral N-acetyl cysteine (NAC) only in patients who receive appropriate fluid and salt loading (2D). We recommend not using oral NAC as the only method for prevention of CIN. (1D)

3.4.4 We do not suggest using theophylline to prevent CIN. (2C)

3.4.5 We do not recommend using fenoldopam to prevent CIN. (1B)

Effects of haemodialysis or haemofiltration

4.5.1: We do not recommend using prophylactic intermittent haemodialysis (IHD) or haemofiltration (HF) for the purpose of prevention of CIN only. (1C)

Rationale

The evidence collected by KDIGO demonstrates that IHD to prevent CIN in well pre-hydrated patients at risk is not effective, and that there is even a trend to more harm (more CIN, and more need for RRT) [73–75]. High-volume HF in this setting has been reported to be beneficial [76, 77]. The protocol used in these studies included HF at ICU, and with high volumes of bicarbonate fluid. It seems likely that under these conditions, the beneficial effects observed were due to volume expansion and loading with bicarbonate rather than to the removal of contrast media by the HF. In view of the high costs and logistical problems, the evidence seems too weak to recommend prophylactic HF at this moment.

Available online at www.sciencedirect.com

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Journal of the Chinese Medical Association 76 (2013) 673–681

www.jcma-online.com

Review Article

Current concepts of contrast-induced nephropathy: A brief review

- One novel technique for the prevention of CIN is removing the majority of the CM from coronary sinuses prior to entering the systemic circulation during coronary angiography. A blood suction catheter is inserted into the coronary sinus via the right femoral vein, and venous blood from the coronary sinus is transferred into a 500-mL contrast-adsorbing column using an extracorporeal system. However, even though the mean calculated iodine removal rate has been reported at 49.4% and this new procedure has been shown to be safe and effective in reducing risk of CIN, a high technique failure rate (57%) currently limits its clinical application.

frontiers in
ENDOCRINOLOGY

MINI REVIEW ARTICLE
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The role of SIRT1 in diabetic kidney disease

Rabi Yacoub, Kyung Lee and John Cijiang He*

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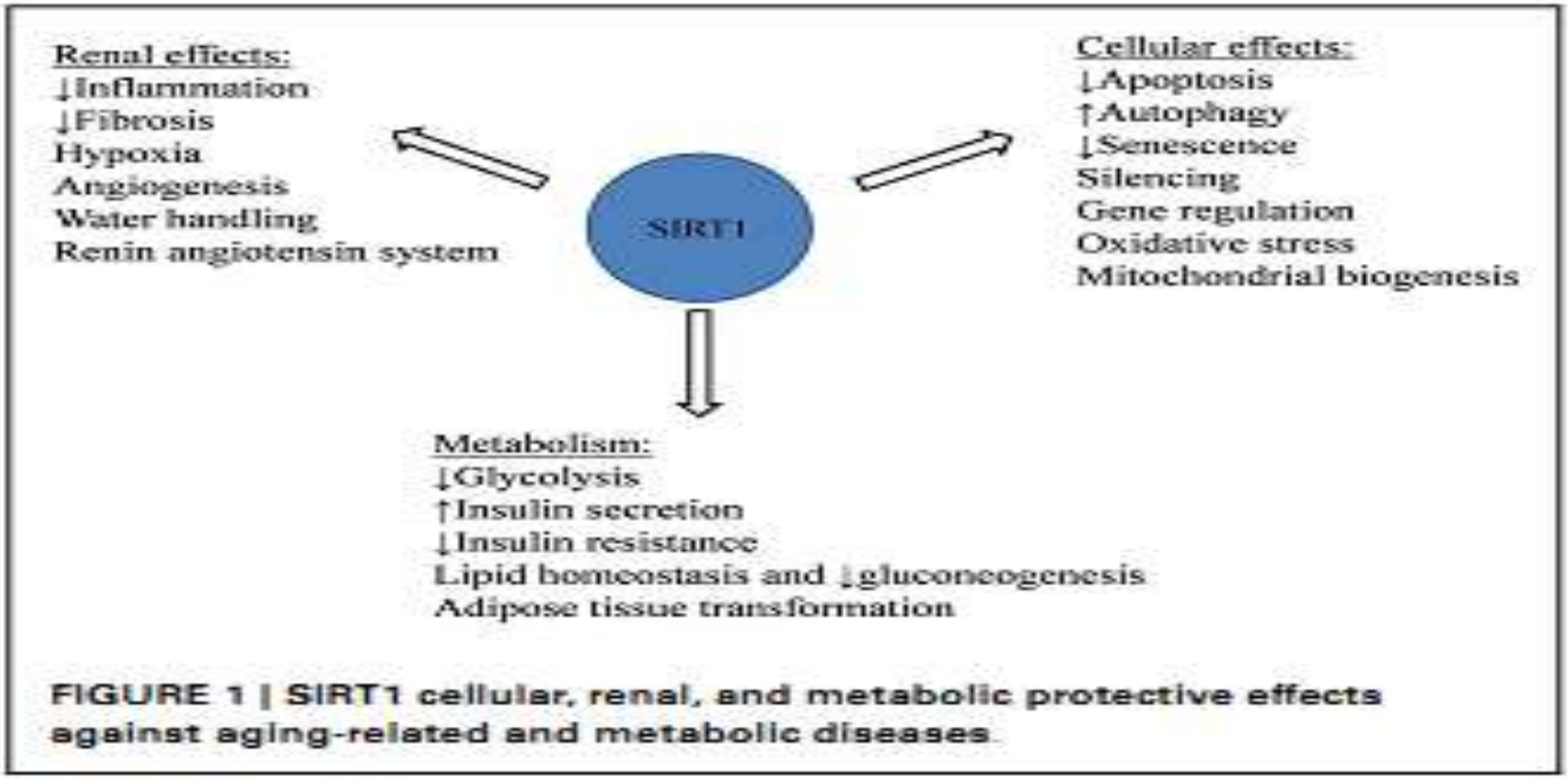

FIGURE 1 | SIRT1 cellular, renal, and metabolic protective effects against aging-related and metabolic diseases.

SIRT1(silent information regulator 1)are NAD-dependent deacetylases

frontiers in
ENDOCRINOLOGY

MINI REVIEW ARTICLE
published: 09 October 2014
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The role of SIRT1 in diabetic kidney disease

Rabi Yacoub, Kyung Lee and John Cijiang He*

Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Mesangial cells	Anti-apoptosis	Attenuates TGF-β1 induced mesangial cell apoptosis through its direct interaction and deacetylation of Smad7
	Inhibition of ROS-mediated apoptosis	P53 deacetylation
	Decreases mesangial expansion	Prevents hyperglycemia-induced hypertrophy by augmenting the AMPK–mTOR signaling pathway
		Binds and activates ACE2 promoter leading to increased Ang1–7 production
Renal medulla	Protects against oxidative injury	Stabilizes HIF-1α and regulates COX2 during intermittent hypoxia-reoxygenation
	Reduces apoptosis and fibrosis	Regulates COX2 decreasing oxidative stress-induced apoptosis
Collecting ducts	Solute and water handling	Represses α-ENaC transcription
Endothelial cells	Prevents early senescence and fibrosis	Upregulates MMP-14 leading to increased matrilytic activity and angiogenesis
	Modulates angiogenesis	Prevents increased permeability and cellular junction disruption via downregulation of VEGF and Flk-1 (in podocytes too)
	Promotes vasodilatation	Decreases the expression of AT1R, and increases NO by deacetylating eNOS
Glomeruli	Attenuates hypoxia-associated mitochondrial damage	Decreases age-associated mtDNA oxidative damages
Renal cortex	Anti-inflammatory	Decreases macrophages infiltrates, deacetylates NF-κB p65 subunit and negatively regulates MCP-1, ICAM-1, and VCAM-1

THANK YOU